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IN

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/927,939	09/11/97	GRAINGER	D 295.022US1

EXAMINER	
MURPHY, J	
ART UNIT	**PAPER NUMBER**
1646	24

HM12/0305
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DATE MAILED: 03/05/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	08/927,939	GRAINGER ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-4,6-11,42 and 43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6-11,42 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *22* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Continued Prosecution Application

The request filed on 12/12/2000 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08927939 is acceptable and a CPA has been established. An action on the CPA follows.

Claims 1, 10, 11 and 42 were amended in Paper No. 21, 12/18/2000. Claims 1, 3-4, 6-11 and 42-43 are pending and under consideration.

Response to Amendment

The rejection of claims 11 and 43 under 35 USC 112, second paragraph for recitation of "cyclic reverse D sequence (CRD)" has been obviated by Applicant's amendment, and is thus withdrawn.

The rejection of claims 1, 3-4 and 6-7 under 35 USC § 102(b) as being anticipated by Rollins et al. (U.S. Patent No. 5,459,128) has been obviated by Applicant's amendment, and is thus withdrawn.

Claim Objections

According to 37 CFR 1.821(d) (MPEP § 2422), where the description or claims of a patent application discuss a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application. Sequences appear in claims 42 but is not identified by SEQ ID NO as required.

Appropriate correction is required.

Claim Rejections - 35 USC § 112 first paragraph

Claims 1, 3-4, 6-11 and 42-43 stand rejected under 35 USC § 112, first paragraph for reasons of records set forth in Paper No. 10, 4/7/1999 and Paper No. 14, 11/12/1999.

Applicant's arguments filed 12/18/2000 have been fully considered but they are not persuasive. Applicant argues that i) the specification provides assays to identify peptides that inhibit a chemokine-induced activity; ii) numerous working examples are provided; iii) the specification provides methods to prepare peptides and structural requirements for activity; iv) the cited Cunningham reference demonstrates skill in the art to identify functionally related peptides; v) the Bowie reference demonstrates proteins are tolerant of amino acid substitutions; vi) the George reference is silent on producing a variant peptide with a certain activity; and vii) claim 6 further limits claim 1.

The unpredictability of the protein art as relates to making substitutions that do not alter the function of the polypeptide, and the sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Mikayama et al. (1993) which teaches that the human glycosylation-inhibiting factor (GIF) protein differs from human migration inhibitory factor (MIF) by a single amino acid residue (page 10056, Figure 1). Yet, despite the fact that these proteins are 90% identical at the amino acid level, GIF is unable to carry out the function of MIF, and MIF does not exhibit GIF bioactivity (page 10059, second column, third paragraph). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Voet et al. (1990) teaches

that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph). These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein.

The Bowie et al. reference further teaches that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). Applicant argues that Bowie shows half of the substitutions are silent. However, given the structural limitations in the claim, i.e. 30 amino acids long, with 3 defined amino acid residues, to make and test all possible combinations with exactly 27 substitution changes would require many different combinations in accordance with the formula:

$$X^n \frac{(L)(L-1)(L-2)...[L-(n-1)]}{n!}$$

wherein, n = number of residues substituted, inserted, or deleted

L = length of polymer

x = number of different types of residues

so that we may calculate, given the limitations of exactly 27 substitutions in the 30 amino acid long polypeptide, would require:

$$27^{20}\frac{(30)(29)(28)(27)(26)...(4)}{27!} = 7.7 \times 10^{41} \text{ different peptides to make and test}$$

This analysis does not take into account all of the combinations further deletions. Assuming half of those are silent, that leaves 3.81×10^{41} peptides.

Based upon the evidence presented in the Bowie et al. reference showing that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex, and the Mikayama et al. and Voet et al. references which demonstrates that the change of a single amino acid can radically alter protein function, and absent sufficient evidence to the contrary it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

Claims 1, 3-4, 6-11 and 42-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claims 1, 3-4, 6-11 and 42-43 define a peptide by a function alone, i.e. it inhibits the activity of the corresponding native chemokine. However, in University of California v. Eli Lilly, 119 F.3 at 1568, 43 USPQ2d at 1406. the Court decided that a definition by function alone "does not suffice" to sufficiently describe a biomolecule "because it is only an indication of what the gene does, rather than what it is." Further, "it is only a definition of a useful result rather that a definition of what achieves that result...The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention". *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

The application on page 27, lines 25-27 sets forth a method of obtaining a chemokine peptide, variant or derivative which inhibits or reduces a chemokine-induced activity. However, in Amgen Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 1206, 18 USPQ2d 1016 at 1022 it was held that "when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e. until after the gene has been isolated". While Applicant has set forth a method for obtaining a chemokine peptide, variant or

derivative which inhibits or reduces a chemokine-induced activity, Applicant has not set forth within the claim the detailed constitution of the chemokine peptide, variant or derivative which inhibits or reduces a chemokine-induced activity, and thus does not satisfy the written description requirement.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-4 and 6-10 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 9520973.

WO 9520973 discloses peptides that bind the IL-1 receptor, and can inhibit binding of IL-1 to its receptor (page 1, lines 12-18). Examples of these peptides that are less than 30 amino acids in length and comprise the claimed WVQ sequence are shown on page 20 line 34 and line 37. An example of a peptide less than 30 amino acids in length that comprises the claimed KQK sequence is on page 25, line 7. The indicated peptides in WO 9520973 correspond to the WVQ and KQK sequences in MCP-1, thus anticipating claim 1. These peptides are not peptides of IL-8 or NAP-2, thus anticipating claim 3. The peptides can be considered a variant of MCP-1, and CC or CXC chemokines, thus anticipating claims 4 and 6-10.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph F. Murphy whose telephone number is 703-305-7245. The examiner can normally be reached on M-F 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
February 15, 2001

Prema Mertz
PREMA MERTZ
PRIMARY EXAMINER